Peginterferon alfa- 2

Brand Name: Pegasys (2a), PEG-Intron (2b)
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Interferons alfa-2a and alfa-2b are biosynthetic forms of interferon alfa and consist of 165 amino acids. Interferons alfa-2a and alfa-2b differ at amino acid position 23; alfa-2a has a lysine in that position, whereas alfa-2b has an arginine at that position. Compared to other interferon alfa subtypes, interferons alfa-2a and alfa-2b both have a deletion at position 44 in the amino acid sequence. [1]

Peginterferon alfa-2a is a covalent conjugate of recombinant alfa-2a interferon with a single branched bis-monomethoxy polyethlyene glycol (PEG) chain. The PEG moiety is linked at a single site via a stable amide bond to lysine. Peginterferon alfa-2b is a covalent conjugate of recombinant alfa-2b interferon with PEG. Interferons alfa-2a and alfa-2b are produced using recombinant DNA technology, through which a human leukocyte interferon gene is inserted into and expressed in Escherichia coli. [2]

The PEG conjugate improves the pharmacokinetic profile of interferon alfa; pegylated interferon alfa clearance is lower than that of non-pegylated interferon alfa. [3]

HIV/AIDS-Related Uses

HIV infected patients are commonly coinfected with hepatitis C virus (HCV). Peginterferon alfa-2a or alfa-2b in conjunction with oral ribavirin is the regimen of choice for the treatment of chronic HCV infection in patients who have not previously received interferon therapy, and the combination regimen is recommended for patients who fail to achieve a sustained virologic response following non-pegylated interferon alfa monotherapy or in combination with oral ribavirin.[4]

Non-HIV/AIDS-Related Uses

Peginterferons alfa-2a and alfa-2b are indicated for use alone or in combination with ribavirin for the treatment of chronic HCV infection in adults who have compensated liver disease and have not been previously treated with interferon alfa.[5]

Pharmacology

The interferon alfa-2a and alfa-2b moieties are responsible for the biological activity of peginterferon alfa. Interferons bind to specific receptors on the cell surface, initiating intracellular signaling via a complex cascade of protein-protein interactions that lead to rapid activation of gene transcription. Interferon-stimulated genes modulate many biologic effects, including the inhibition of viral replication in infected cells, inhibition of cell proliferation, and immunomodulation (e.g., enhancement of phagocytic activity of macrophages, augmentation of specific cytotoxicity of lymphocytes for target cells, inhibition of virus replication in virus-infected cells). Peginterferon alfa stimulates the production and raises concentrations of effector proteins; raises body temperature; and causes reversible decreases in leukocyte and platelet counts.[6] [7] [8]

After subcutaneous (SC) administration of peginterferon alfa-2a, maximal serum concentrations (Cmax) occur between 72 to 96 hours postdose. The Cmax and area under the plasma concentration-time curve (AUC) measurements increase in a dose-related manner. Week 48 mean trough concentrations at 168 hours postdose are approximately twofold higher than Week 1 mean trough concentrations (16 ng/ml versus 8 ng/ml, respectively). Steady state serum levels are reached within 5 to 8 weeks of once weekly dosing. The mean systemic clearance of peginterferon alfa-2a in healthy subjects was 94 ml/h, which is approximately 100-fold lower than that for nonpegylated interferon alfa-2a. The mean terminal half-life after SC dosing in patients with chronic HCV was 80 hours (range 50 to 140 hours). In comparison, the mean terminal half-life of the nonpegylated interferon alfa-2a was 5.1 hours (range 3.7 to 8.5 hours).[9]

The absorption half-life for peginterferon alfa-2b is 4.6 hours.[10] After SC administration of peginterferon alfa-2b, Cmax occurs between 15 to 44 hours postdose and is sustained for up to 48 to 72 hours. Cmax and AUC values increase in a dose-related manner. After multiple dosing, there is an increase in bioavailability. Week 48 mean trough concentrations are approximately 3 times

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Pharmacology (cont.)

higher than Week 4 mean trough concentrations. The mean peginterferon alfa-2b elimination half-life is approximately 40 hours (range 22 to 60 hours) in patients with HCV infection. Renal elimination accounts for 30 percent of the clearance, and impaired renal function (creatinine clearance less than 50 ml/minute) leads to a significant reduction in drug clearance.[11]

Peginterferon alfa (used alone) is in FDA Pregnancy Category C. There have been no adequate or well-controlled studies of peginterferon alfa-2 in pregnant women. Although no teratogenic effects occurred in laboratory animals whose offspring were delivered at term, there was a significant increase in spontaneous abortions seen with use of both peginterferons alfa-2a and alfa-2b. Peginterferon alfa should be assumed to have abortifacient potential and should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.[12] [13]

Peginterferon alfa-2/ribavirin combination therapy is in FDA Pregnancy Category X. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Use of peginterferon alfa with ribavirin is contraindicated in women who are pregnant or in the male partners of women who are pregnant. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.[14] [15]

It is not known whether peginterferons alfa-2a and alfa-2b are excreted into breast milk, but because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue the treatment, taking into account the importance of the product to the mother.[16] [17]

In patients with end-stage renal disease undergoing hemodialysis, there is a 25% to 45% reduction in peginterferon alfa-2a clearance, resulting in correspondingly higher exposure to the drug. Patients should be monitored for symptoms of interferon toxicity and may require dose reduction.[18] Renal elimination of peginterferon alfa-2b is approximately 30%, with clearance possibly reduced by one-half in patients with renal function impairment.[19] Both peginterferon alfa-2a and alfa-2b should be used with caution in patients with creatinine clearances less than 50 ml/min.[20] [21]

Adverse Events/Toxicity

Adverse effects associated with use of peginterferon alfa include anxiety; depression; emotional lability; fever; hemorrhagic or ulcerative colitis; hepatomegaly; viral infection; insomnia; irritability; neutropenia; pancreatitis; thrombocytopenia; and hypothyroidism. Some lesser side effects that may not need medical attention include abdominal pain; alopecia; anorexia; cough; diarrhea; dizziness; dry skin; dyspepsia; fatigue; flu-like symptoms; flushing of skin; headache; injection site reaction; malaise; musculoskeletal pain; nausea; pharyngitis; rigors; sinusitis; skin rash or itching; increased sweating; vomiting; and weight loss.[22]

Nearly all study patients in clinical trials involving peginterferon alfa-2a or alfa-2b experienced one or more adverse events.[23] [24] Peginterferon use may cause or aggravate life-threatening or fatal neuropsychiatric, autoimmune, ischemic, and infectious reactions. Patients should be monitored closely with periodic clinical and laboratory evalulations. Patients with persistent severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after peginterferon alfa therapy is discontinued. Use of peginterferon alfa with ribavirin may cause a broad variety of serious adverse reactions, including birth defects and/or death of the fetus. Ribavirin also causes hemolytic anemia.[25] [26]

The most common reasons for dose modification or withdrawal from studies were hematologic abnormalities (e.g., anemia, neutropenia). Incidences of adverse hematologic effects appear to be greater in patients receiving concomitant therapy with peginterferon alfa and oral ribavirin than in those receiving peginterferon alfa monotherapy.[27]

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Drug and Food Interactions

Peginterferons alfa-2a and alfa-2b inhibit cytochrome P450 (CYP450) 1A2 enzymes. They do not affect the pharmacokinetics of drugs metabolized by CYP450 2C9, 2C19, 2D6, or 3A4 hepatic microsomal enzymes.[28] [29] Coadministration of peginterferon alfa with theophylline, which is metabolized by CYP450 enzymes, resulted in a 25% increase of theophylline serum concentrations. Routine monitoring of plasma theophylline concentrations and appropriate dosage adjustments are recommended. Coadministration of ribavirin (as a common adjunct to peginterferon alfa) and didanosine is not recommended. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis, have been reported in clinical trials. Ribavirin also antagonizes the in vitro antiviral activity of stavudine and zidovudine, so concomitant use of treatments containing ribavirin with either of these drugs should be avoided.[30]

Contraindications

Use of peginterferons alfa-2a and alfa-2b is contraindicated in patients with autoimmune hepatitis, hepatic decompensation (Child-Pugh class B and C) before or during treatment, or hypersensitivity to the drug or any of its components. Combination therapy with peginterferons alfa-2a or alfa-2b and ribavirin is also contraindicated in women who are pregnant, men whose female partners are pregnant, and in patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia).[31] [32] [33]

Risk-benefit should be considered in patients with autoimmune diseases (e.g., interstitial nephritis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, thrombocytopenia, thyroiditis); cardiovascular diseases; diabetes mellitus, hyperglycemia, hyperthyroidism, or hypothyroidism; psychiatric disorders; pulmonary function impairment or pulmonary infiltrates; or renal function impairment.[34]

Additionally, peginterferon alfa-2a formulations contain benzyl alcohol and are therefore contraindicated in neonates and infants. Benzyl alcohol is associated with an increased incidence of neurologic and other complications, sometimes fatal, in neonates and infants.[35] [36]

Clinical Trials

For information on clinical trials that involve Peginterferon alfa-2, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Peginterferon alfa-2 AND HIV Infections.

Dosing Information

Mode of Delivery: Subcutaneous.[37]

Dosage Form: Peginterferon alfa-2a: single use 1.0-ml vials containing the equivalent of 180 mcg peginterferon alfa-2a.[38] [39]

Peginterferon alfa-2b: powder for injection in 0.5-ml vials, containing the equivalent of 50, 80, 120, and 150 mcg peginterferon alfa-2b.[40] [41]

Storage: Peginterferon alfa-2a should be stored in the refrigerator at 2 C to 8 C (36 F to 46 F), should not be frozen or shaken, and should be protected from light.[42]

Peginterferon alfa-2b powder for injection should be stored at 25 C (77 F), with excursions permitted at 15 C to 30 C (59 F to 86 F), and should not be frozen.[43]

Chemistry

CAS Number: 215647-85-1 (2b)[44]

Molecular weight: 60,000 daltons (2a); 31,000 daltons (2b)[45]

Physical Description: Peginterferon alfa-2a solution is colorless to light yellow, with a pH of 6.0 +/- 0.5.[46]

Peginterferon alfa-2b is a white to off-white lyophilized powder.[47] Reconstituted solutions of peginterferon alfa-2b are clear, colorless, and contain no preservative.[48]

Stability: Vials of peginterferon alfa-2a solution are

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Chemistry (cont.)

for single use only; any unused portion should be discarded.[49]

After reconstitution of the powder with the supplied diluent, peginterferon alfa-2b solution should be used immediately, but may be stored up to 24 hours at 2 C to 8 C (36 F to 46 F). The reconstituted solution contains no preservative.[50]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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